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THE EFFECT OF THE ROENTGEN RAY AND MUSTARD GAS (DICHLORETHYLSULPHID) ON ACTIVE ANAPHYLAXIS IN THE GUINEA-PIG

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The importance attributed to allergy in the resistance to tuberculosis makes it advisable to study this state in as many ways as possible. In view of the report that certain leukotoxic agents, notably benzene and the roentgen ray, influence the allergic condition, a way seemed open to gain information as to the importance of allergy in the resistance to tuberculosis, especially as the guinea-pig is susceptible to both tuberculosis and sensitization. Corper¹ failed to note any effect from thorium x, another leukotoxic agent, on active anaphylaxis in the guinea-pig, while v. Heinrich² concluded that the formation of "sensibilisin" was reduced markedly by the roentgen ray, and was most marked when guinea-pigs were treated with the roentgen ray immediately after the sensitizing injection, the reinjection of foreign protein being given 3 weeks later, coincident with the maximum destructive effect of the roentgen ray on the lymphoid tissues. If the reinjection was given 6 weeks after treatment with the roentgen ray, the effect on the anaphylactic reaction was much less marked. The protein solution, horse serum, was used in amounts of 0.01 c c for sensitizing and from 0.05 to 0.5 c c for the second injection.

ROENTGEN-RAY EXPERIMENTS

The study reported was carried out on young male guinea-pigs weighing from about 250 to 300 gm. each, and the roentgen ray was given in three different doses as shown in the tables. Two separate protein mixtures, egg white and fresh normal horse serum were used to produce active anaphylaxis; in both cases the first injection consisted of 0.1 c c of sterile protein mixture mixed with 0.1 c c of sterile 0.9% sodium chloride solution, while the second injection was 1.0 c c of the sterile protein mixture and 1.0 c c of salt solution. These two proteins were chosen because in the doses used the egg white

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¹ Jour. Infect. Dis., 1919, 25, p. 248.

² Centralbl. f. Bakteriol, O., 1, 1913, 70, p. 421.

produces a severe and frequently fatal anaphylaxis while the normal horse serum usually produces a definite but not fatal anaphylaxis, hence the effect of treatment with the roentgen ray on the anaphylactic reaction in the guinea-pigs could be noted easily. Leukocyte counts were made every second day to note the effect of the roentgen ray on the circulating leukocytes during the experiments. The results of these experiments with egg white are given in table 1. It is to be

TABLE 1
THE EFFECT OF ROENTGEN RAYS ON ANAPHYLAXIS IN THE GUINEA-PIG PRODUCED BY
EGG WHITE *

Experiments	Roentgen-Ray Treatment		Maximum Reaction	Time of Maximum Reaction After Injection, Minutes	Lowest Leukocyte Count Attained	Time in Days of Lowest Leukocyte Count After Sensitization	Leukocyte Count on Day of Second Protein Injection
	Exposure	When Given					
Single large exposure	22 cm. spark gap; 5 milliamperes; target 30 cm. away, 15 minutes†	7 days before the first protein injection	+++ Died ++	30 9 45	3,200 3,000 4,800	4 0 4	9,400 10,600 8,400
		On same day as first injection	+++ Died +	40 35 60	4,000 5,600 4,800	10 6 10	10,200 11,400 8,600
Repeated medium exposures	17 cm. spark gap; 5 milliamperes; target 30 cm., 15 minutes	Began 7 days before sensitization and repeated every 3 days to keep circulating leukocytes at a low level	Died +++ Died	75 45 30	2,000 2,200 1,400	17 15 9	2,200 2,800 1,800
Repeated small exposures	8 cm. spark gap; 1 milliampere; target 30 cm., 3 minutes	Began 2 days before sensitization and repeated every 3 days throughout experiment	++ +++ +++ ++	35 45 (died in 3 hours) 40 60	7,600 10,600 8,200 8,000	12 16 12 18	8,200 10,600 8,900 9,200
Single large exposure	22 cm. spark gap; 5 milliamperes; target 30 cm., 15 minutes	7 days before the second protein injection	+++ Died Died	35 20 60	5,600 6,200 6,000	19 18 18	5,600 6,400 6,200
		On same day as second protein injection	+++ +++ +++ ++	45 35 45 20	8,000 11,000 12,400 12,400
Controls...	+++ +++ +	40 25 45			

* The anaphylactic reaction obtained after the second protein injection is graded from — no reaction, mild +, moderate ++, and +++ a severe reaction with subsequent recovery of the animal. When the guinea-pig died during the acute reaction it is designated by "died." The interval between the first and second injection of egg white was 19 days. The first injection of protein, given intraperitoneally was 0.1 cc of egg white with 0.1 cc of salt solution and the second injection, given intraperitoneally, was 1 cc of egg white with 1 cc of salt solution.

† In the experiments in which the 22 cm. spark gap, 5 milliampere current for 15 minutes, or the 17 cm. spark gap, 5 milliampere current for 15 minutes, was used the exposure was made at 3 minute intervals with a 10 minute rest to cool the Coolidge tube.

noted that the maximum nonlethal dose of roentgen ray given before (7 days) or coincident with the first injection of egg white, or before (7 days) or with the second injection, had no ameliorating influence on the anaphylactic reaction after the second injection. Likewise,

TABLE 2
THE EFFECT OF ROENTGEN RAYS ON ANAPHYLAXIS IN THE GUINEA-PIG PRODUCED BY
NORMAL HORSE SERUM *

Experiments	Roentgen-Ray Treatment		Maximum Reaction	Time of Maximum Reaction After Injection, Minutes	Lowest Leuko- cyte Count Attained	Time in Days of Lowest Leukocyte Count After Sensitization	Leuko- cyte Count on Day of Second Protein Injection	
	Exposure	When Given						
Single large exposure	22cm. spark gap; 5 milliamperes; target 30 cm. away, 15 minutes	7 days before the first protein injection	+++ Died ++	45 50 45	5,200 2,800 3,400	8 1 3	9,200 8,000 8,600	
		On same day as first injection	++ ++ +	50 35 50	6,000 5,600 4,400	6 9 8	12,000 8,800 10,400	
		Repeated medium exposures	17cm. spark gap; 5 milliamperes; target 30 cm., 15 minutes	Began 7 days before sensitization and repeated every 3 days to keep circulating leukocytes at a low level	++ + ++	50 (died in 2.5 hours) 50 30	2,200 1,200 1,000	17 2 8
Repeated small exposures	8 cm. spark gap; 1 milliampere; target 30 cm., 3 minutes		Began 2 days before sensitization and repeated every 3 days throughout experiment	++ ++ + +++	25 40 45 25	10,000 8,200 8,400 9,600	7 17 7 12	10,200 8,200 8,800 10,000
	Single large exposure		22 cm. spark gap; 5 milliamperes; target 30 cm., 15 minutes	7 days before the second protein injection	++ +++ ++ +++	45 35 30 45	7,200 5,800 6,000 7,200	19 17 19 17
			On same day as second protein injection	++ +++ ++ ++	50 35 25 40	10,200 10,200 12,400 9,800
Controls...			+++ ++ + +	30 25 45 30		

* The anaphylactic reaction is graded as in table 1, from — to +++. The interval between the first and second injection of normal horse serum was 19 days. The first injection of protein given intraperitoneally was 0.1 cc of normal horse serum with 0.1 cc salt solution and the second injection of protein given intraperitoneally was 1 cc of normal horse serum with 1 cc of salt solution.

repeated moderate roentgen-ray treatments, sufficient to maintain the circulating leukocytes at about 2000 per c. mm. of peripheral blood, throughout the incubation period, or very small repeated treatments not noticeably affecting the peripheral leukocytes, had no appreciable

ameliorating effect on the anaphylactic reaction. On the contrary, a slight increase in the severity of the reaction was noted, especially in those animals given the second injection when the roentgen ray had exerted a more profound effect as indicated by the level of the peripheral circulating leukocytes.

The results obtained with normal horse serum and roentgen-ray treatments were similar to those obtained with egg white and are given in table 2. The anaphylactic reaction following the second intraperitoneal injection of normal horse serum did not seem to be inhibited or reduced in the guinea-pigs that had been treated with the roentgen ray regardless of whether the treatment was a single large dose 7 days before or coincident with the first injection of horse serum, or before (7 days) or coincident with the second dose of serum. Repeated exposures to the roentgen ray sufficient to maintain a decided leukopenia throughout the incubation period or exposures insufficient to appreciably affect the peripheral leukocytes had no determinable effect on the anaphylactic reaction. When, however, the roentgen ray had exerted a profound effect on the hematopoietic system, as indicated by the reduction in the number of peripherally circulating leukocytes, the severity of the anaphylactic reaction seemed to be slightly increased.

MUSTARD GAS EXPERIMENTS

Mustard gas came into prominence as a result of its use in warfare and although its specific toxic action on the skin, conjunctiva and respiratory tract were recognized early, its action on the hematopoietic system remained undisclosed for some time. Krumbhaar and Krumbhaar³ noted a direct toxic action on the bone marrow in gassed men, resulting in a depletion of the circulating leukocytes preceded by a preliminary leukocytosis. Pappenheimer and Vance⁴ obtained similar results in rabbits; these findings were corroborated by Hektoen and Corper,⁵ who found that mustard gas also has an inhibitory action on the development of specific antibodies in both rabbits and dogs, placing it in a class with leukotoxic agents like benzene, the roentgen ray and thorium x.

The study with mustard gas was carried out on young male guinea-pigs. The mustard gas was administered in solution, in 50%

³ Jour. Amer. Med. Assn., 1919, 72, p. 39, and Jour. Med. Res., 1919, 40, p. 497.

⁴ Jour. Exper. Med., 1920, 31, p. 72.

⁵ Jour. Infect. Dis., 1921, 28, p. 279.

glycerol in 0.9% Na Cl solution, subcutaneously in 3 different doses as shown in the tables. The proteins used to produce anaphylaxis were egg white and normal horse serum, the mode of administration and dosage being the same as in the roentgen-ray experiments. Leukocyte

TABLE 3
THE EFFECT OF MUSTARD GAS ON ANAPHYLAXIS IN THE GUINEA-PIG PRODUCED BY
EGG WHITE *

Experiments	Mustard Gas Injections		Maximum Reaction	Time of Maximum Reaction After Injection, Minutes	Lowest Leukocyte Count Attained	Time in Days of Lowest Leukocyte Count After Sensitization	Leukocyte Count on Day of Second Protein Injection
	Dose	When Given					
Single large dose	0.5 c c 0.2%	7 days before the first protein injection	Died	40	5,200	8	9,200
			+++	50	8,200	4	10,400
			+++	30	8,000	15	12,800
			+++	55	9,800	4	11,200
			+++	50	7,800	9	10,400
Repeated medium doses	0.5 c c 0.02%	On same day as first injection	+++	40	9,600	6	12,000
			+++	45	6,000	8	12,400
			+++	40 (died in 3 hours)	4,000	12	10,400
			+++	55	6,600	15	7,200
			+++	55	6,000	12	7,800
Repeated small doses	0.5 c c 0.002%	Began 5 days before sensitization and repeated every 3 or 4 days throughout experiment	Died	80	9,600	4	12,400
			+++	45	6,000	8	10,400
			+++	40 (died in 3 hours)	4,000	12	7,800
			+++	55	6,600	15	7,200
			+++	55	6,000	12	7,800
Single large dose	0.5 c c 0.2%	Began 3 days before sensitization and repeated every 3 days throughout experiment	+++	40	6,200	20	6,200
			Died	55	8,400	12	9,200
			+++	45	9,400	4	14,800
			Died	105	6,000	12	8,000
			+++	40	6,200	20	6,200
Single large dose	0.5 c c 0.2%	7 days before the second protein injection	+++	35	10,000	17	10,000
			+++	45	7,200	17	8,000
			Died	2 hours	10,000	20	10,000
			+++	50	6,200	17	8,400
			+++	75	11,800
Controls...	Died	25	10,000
			+++	45 (died in 3 hours)	13,600
			+++	55	13,800
			+++	55	13,800
			Died	75	13,800
Controls...	+++	40	13,200
			Died	35	8,800
			+++	55	10,800
			+++	55	10,800
			Died	75	12,400

* The anaphylactic reaction in this table and table 4 is graded as in table 1, from — to +++. The interval between the first and second injection of egg white was 20 days. The first injection of protein given intraperitoneally was 0.1 c c of egg white with 0.1 c c salt solution and the second injection of protein given intraperitoneally was 1 c c of egg white with 1 c c of salt solution.

counts were made every second day during the experiments, the last count on the day of and preceding the second protein injection. The results of these experiments are given in tables 3 and 4.

Mustard gas does not produce as profound effects on the leukocytes in the guinea-pig as the roentgen ray or thorium x, especially in doses consistent with the life of the animal, and it may produce a leukocytosis. The results seem to indicate, however, that like the roentgen ray and thorium x, mustard gas has no appreciable influence on the allergic or anaphylactic reaction whether given subcutaneously 7 days before

TABLE 4
THE EFFECT OF MUSTARD GAS ON ANAPHYLAXIS IN THE GUINEA-PIG PRODUCED BY
NORMAL HORSE SERUM

Experiments	Mustard Gas Injections		Maximum Reaction	Time of Maximum Reaction After Injection, Minutes	Lowest Leukocyte Count Attained	Time in Days of Lowest Leukocyte Count After Sensitization	Leukocyte Count on Day of Second Protein Injection
	Dose	When Given					
Single large dose	0.5 c c 0.2%	7 days before the first protein injection	+++	40 (died in 3 hours)	5,000	8	12,000
			+++	60	6,800	2	11,200
		On same day as first injection	+++	35	6,200	9	9,600
			+++	60	8,200	6	10,000
			+++	60	9,400	9	14,800
			++	40	6,600	6	9,200
Repeated medium doses	0.5 c c 0.02%	Began 5 days before sensitization and repeated every 3 or 4 days throughout experiment	+++	45	8,000	8	11,000
			+++	50	6,000	15	6,200
			Died	110	6,000	12	10,600
			+++	60	8,400	8	9,000
Repeated small doses	0.5 c c 0.002%	Began 3 days before sensitization and repeated every 3 days throughout experiment	++	45	9,800	15	11,600
			+++	35	8,400	15	12,800
			+++	55	7,000	4	9,800
			+++	45	5,200	4	10,200
Single large dose	0.5 c c 0.2%	7 days before the second protein injection	++	60	7,400	20	7,400
			Died	90	7,200	20	7,200
			++	45	9,600	15	11,200
			+++	50	9,000	17	9,400
		On same day as second protein injection	++	35	10,000
Controls...	++	55	8,200
			+++	60	14,200
			+++	50	7,600
Controls...	+++	40	9,600
			++	50	11,400
			+++	60 (died in 3 hours)	12,000
			+++	45	10,000

or coincident with the first protein injection or 7 days before or with the second injection, in maximum nonlethal doses. Likewise, repeated small or medium doses throughout the entire incubation period and initiated a few days before the primary injection are without appreciable effect.

DISCUSSION

Von Heinrich² was inclined to view his results as indicating that the roentgen ray restrained the formation of the "sensibilisin" by its action on the lymphoid tissues and interference with antibody formation. If we were certain that anaphylaxis is of antigen-antibody nature, we might be able to draw more definite conclusions regarding the effect of the roentgen ray on the antibodies concerned. Hektoen and his colleagues⁶ found that not all antibodies were affected equally by leukotoxic agents; thorium x may interfere with the production of precipitin but not of lysin. Thus we are confronted with the possibility that the antibodies, if such they are, involved in the complicated reaction of anaphylaxis may belong to the class of those not appreciably influenced in vivo by the roentgen ray, or it may be that the crudeness of the quantitative estimation in the anaphylactic reaction makes it impossible to detect slight differences as is possible in the estimations of lysins, precipitins and agglutinins. There is another consideration to which Corper¹ called attention in his work on thorium x and anaphylaxis, namely, that we are dealing with a chronic poisoning by the roentgen ray, whose action, combined with that of the anaphylaxis may slightly increase the severity of the latter, especially when the reaction is precipitated at the height of the action of the roentgen ray.

SUMMARY

In guinea-pigs a maximum nonlethal dose of roentgen ray given 7 days before or coincident with the sensitizing injection of egg white or normal horse serum, or 7 days before or with the second injection, causes no appreciable ameliorating influence on the reaction resulting from the second injection of these proteins. Likewise, repeated moderate roentgen ray treatments, sufficient to maintain a low level of the peripheral circulating leukocytes, about 2,000 leukocytes per c mm, throughout the incubation period, or very small repeated treatments not noticeably affecting the number of peripheral circulating leukocytes, has no appreciable ameliorating effect on the severity of the anaphylactic reaction. A slight increase in the severity of the reaction was noted, however, especially in guinea-pigs given the second or exciting injection of protein when the roentgen ray had exerted a profound influence on the hematoipoetic system as indicated by the

⁶ Jour. Infect. Dis., 1916, 19, p. 69; 1915, 17, p. 415; 1918, 22, p. 28; 1920, 26, p. 330.

level of the leukocytes. As pointed out by Corper in the case of thorium x and anaphylaxis, this result may be due to the intoxication with the roentgen ray coincidently with the anaphylactic reaction.

Subcutaneous injections of mustard gas in maximum nonlethal doses given 7 days before or coincident with the sensitizing injection of egg white or normal horse serum, or 7 days before, or with the second injection, are without appreciable influence on the reaction resulting from the second injection of these proteins. Likewise, repeated small or medium doses administered throughout the incubation period, being initiated a few days before the first protein injection, are without appreciable effect.